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ORIGINAL ARTICLE

Influence of different types of low substituted hydroxypropyl cellulose on tableting, disintegration, and floating behaviour of floating drug delivery systems

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Sodium alginate

Abstract The object of the present study is to evaluate the effect of application of low-substituted hydroxypropyl cellulose (L-HPC) 11 and B1 as excipients promoting floating in gastroretentive tablets. Directly compressed tablets were formed based on experimental design. Face-centred central composite design was applied with two factors and 3 levels, where amount of sodium alginate (X_1) and L-HPC (X_2) were the numerical factors. Applied types of L-HPCs and their 1:1 mixture were included in a categorical factor (X_3). Studied parameters were floating lag time, floating time, floating force, swelling behaviour of tablets and dissolution of paracetamol, which was used as a model active substance. Due to their physical character, L-HPCs had different water uptake and flowability. Lower flowability and lower water uptake was observed after 60 min at L-HPC 11 compared to L-HPC B1. Shorter floating times were detected at L-HPC 11 and L-HPC mixtures with 0.5% content of sodium alginate, whereas alginate was the only significant factor. Evaluating results of drug release and swelling studies on floating tablets revealed correlation, which can serve to help to understand the mechanism of action of L-HPCs in the field development of gastroretentive dosage forms.

1. Introduction

Floating drug delivery systems belong to the group of gastroretentive dosage forms firstly described by Davis in 1968 (Davis, 1968). These dosage forms are able to achieve prolonged gastric residence time with increased period for active pharmaceutical ingredients (API) to be released. Action can be local for treatment of the stomach or may be systemic. In the development of floating dosage forms, two different technologies are applied based on

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their mechanism of buoyancy. Various types of effervescent and non-effervescent approaches have been discussed by Singh et al. (Singh and Kim, 2000). In our experiments, effervescent floating tablets (EFT) were prepared based on sodium alginate as a swelling agent and sodium hydrogen carbonate generating carbon dioxide in the acidic media. During the swelling of sodium alginate, carbon dioxide is entrapped in a hydrating gel frame leading to drop of internal density, which leads to the buoyancy of the preparation. One of the most important aims of application of floating drug delivery systems is the fact that several drugs have only narrow absorption window in the gastrointestinal tract, which raises difficulties during the enhancement of the bioavailability. Prolonged gastric residence is also reasonable for drugs which are unstable in the lower section of the gastrointestinal tract or having poor absorption from intestines (Srivastava et al., 2005). In our experiments, sodium alginate floating matrix tablets were produced by simple direct compression.

Mechanisms of different types of disintegrants applied in floating tablets have various effects including swelling, particle repulsion as well as gas generation (Rudnic et al., 1982). Low-substituted hydroxypropyl cellulose (L-HPC) is a widely used disintegrant in direct compression of tablets and granulation as well. Applied concentration is generally between 2.5% and 5.0% (Kawashima et al., 1993a,b). Its disintegrating effect is due to its rapid and intense water uptake and swelling, in which the dominant parameter is the particle size described by Kawashima et al. (1993a,b) as well as shape of particles controlling the process of disintegration.

Another commonly applied excipient in gastroretentive tablets is sodium alginate, which is a non-toxic, biodegradable co-polymer composed of L-guluronic and D-mannuronic acid blocks (Whitehead et al., 1998) derived from brown seaweed species and extracted by the ion-changing technique (Miller, 1996). Sodium alginate also hydrates and swells in aqueous media, however in acidic medium insoluble alginic acid is formed which contributes to the buoyancy.

In the present study the nonsteroidal anti-inflammatory drug (NSAID), paracetamol was used as a model API, which is a widely applied analgesic and antipyretic agent, acting by the inhibition of COX 3 enzyme (Botting and Ayoub, 2005). Paracetamol is highly metabolized, its mean plasma half-life is 2 h in healthy adults (Thomas, 1993), therefore preparation of a floating drug delivery system containing paracetamol is also reasonable. Its solubility is high, 20.2 mg/ml in 0.1 M HCl, therefore its dissolution from matrix tablets is considered to be independent from solubility properties (Obeidat et al., 2010).

In the present study EFTs were prepared according to an experimental design including categorical face-centred central composite set-up with two numeric factors (concentration of sodium alginate and L-HPC) having three levels with one centre point. To accomplish the difference between L-HPC types, categorical factor was introduced, including the two types of L-HPC applied and their 1:1 mixture. Linear, quadratic and cubic fitting models were assessed on the responses in order to find the best model to evaluate the results.

2. Materials and methods

2.1. Materials

Paracetamol (Molar Chemicals, Hungary) was used as a model drug substance. High viscosity sodium alginate (Hungaropharma, Hungary) was used as the swelling excipient promoting flotation. Viscosity of the applied 1% sodium alginate solution was 213.80 ± 0.83 mPas measured at 100 s^{-1} shear rate with Anton Paar Rheolab QC viscometer at 30 °C. Low substituted hydroxypropyl cellulose B1 (Egis Pharmaceuticals PLC, Hungary) and 11 (Egis Pharmaceuticals PLC, Hungary) were used as disintegrants. Sodium bicarbonate (Molar Chemicals, Hungary) was used as effervescent agent. Talc, magnesium stearate, microcrystalline cellulose and silica colloidal anhydrous were used as excipients for tablet compression (Hungaropharma, Hungary).

2.2. Comparative physical examination of L-HPC 11 and L-HPC B1 disintegrants

2.2.1. Microscopic examination

Microscopic examination at 160× and 640× magnification (Zeiss, Axio Imager A1 Microscope, Germany) was performed to measure particle size and shape parameter of the two different types of L-HPCs by using a 5 megapixel microscopic camera (Zeiss AxioCam MRc 5, Germany). For particle size examination 50 largest separated particles were measured.

Sphericity (Ψ) was calculated by the following formula:

$$\Psi = 4\pi \frac{A_f}{P_{Cr}^2} \quad (1)$$

Sphericity of particles describes the form of region on the bases of their circularity. Numerically range is from 0 to 1. The value of the sphericity for a perfect round shape particle is 1. Filled area (A_f) is the region including any holes on it. Crofton perimeter (P_{Cr}) determines circular region with correction, which is optimized for circular objects. For digital photo analysis Zeiss Axio Vision Rel. 4.7 software (Carl Zeiss, Germany) was used.

2.2.2. Flowability

Differences in flow properties of the types of L-HPCs were examined to highlight further physical dissimilarities. Determination of angle of repose was carried out according to 2.9.16. test of Ph. Eur. 5.0. During the examinations ASTM standard funnel was used having 111 mm height and 10 mm size of orifice. The funnel was fixed 4 cm above a glass plate. Measurement was carried out in triplicate. Angle of repose was calculated by the following formula (USP, 2007):

$$tg(\alpha) = \frac{H}{R} \quad (2)$$

where, α is the angle of repose, H is the height above the glass plate, and the R is the radius of the conical pile. Result was considered to be valid, when symmetric cone shape was formed.

Apparent density examination was carried out by a volumetric device (Erweka SVM 121, Germany) according to 2.9.15. Ph. Eur. 5.0. During the experiments tapped and bulk densities were calculated. 100.0 g L-HPC types were filled into a dry graduated cylinder, after which the cylinder was locked on a tapping platform performing 10, 500, and 1250 taps. Bulk densities (ρ_{bulk}) were recorded after filling into graduated cylinder; tapped densities (ρ_{tapped}) were recoded after 1250 taps referred to 100.0 g sample. Using these measurements Carr index (C_i) (Carr, 1965) was calculated according to the following formula: